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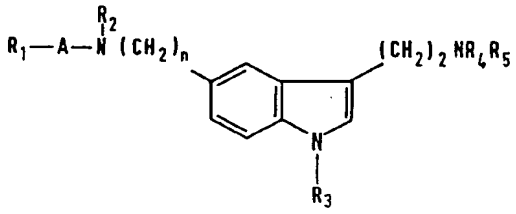
(58) Field of search
C2C

(54) Pharmaceutically active 5-acylaminoalkyl-3-aminoalkyl-1H-indoles

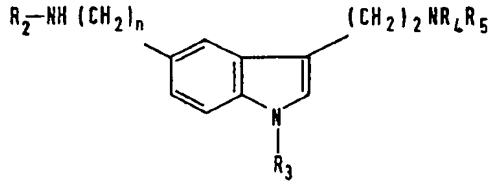
(57) Novel compounds of formula (I):



(I)

wherein R_1 is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, or phenyl (C_{1-4}) alkyl,
R_2 and R_3 are independently H or C_{1-3} alkyl,
R_4 and R_5 are independently H, C_{1-3} alkyl or 2-propenyl;
A is $-CO-$ or $-SO_2-$,
n is 2 to 5, provided that R_1 is not H when A is $-SO_2-$,
and physiologically acceptable salts and solvates e.g. hydrates thereof have potent and selective vasoconstrictor activity and are indicated as useful for the treatment of migraine.

Intermediates of formula II



(II)

are also claimed.

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SPECIFICATION

Chemical compounds

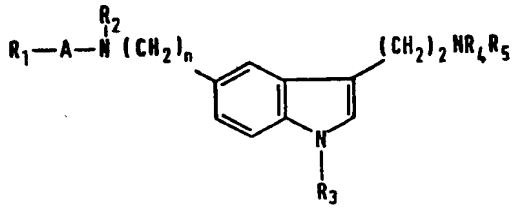
This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

The pain of migraine is associated with excessive dilatation of the cranial vasculature, and known treatments for migraine include the administration of compounds having vasoconstrictor properties, such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and dangerous side effects. Migraine may also be treated by administering an analgesic, usually in combination with an antiemetic, but such treatments are of limited value.

There is thus a need for a safe and effective drug for the treatment of migraine, which can be used either prophylactically or to alleviate an established headache, and a compound having a selective vasoconstrictor activity would fulfil such a role.

We have now found a group of indole derivatives having potent and selective vasoconstrictor activity.

The present invention provides an indole of the general formula (I):



(I)

wherein

R_1 represents a hydrogen atom, a C_{1-6} alkyl or C_{3-7} cycloalkyl group, or a phenyl or phenyl (C_{1-4}) alkyl group;

R_2 represents a hydrogen atom or a C_{1-3} alkyl group;

R_3 represents a hydrogen atom or a C_{1-3} alkyl group;

R_4 and R_5 which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group or a 2-propenyl group;

A represents $-CO-$ or $-SO_2-$;

and n represents an integer from 2 to 5; (with the proviso that R_1 does not represent hydrogen when A represents $-SO_2-$) and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The invention includes within its scope all optical isomers of compounds of formula (I) and their mixtures, including the racemic mixtures thereof.

Referring to the general formula (I), the alkyl groups may be straight chain or branched chain alkyl groups, such as methyl, ethyl or isopropyl groups. The cycloalkyl group may be for example a cyclopentyl or cyclohexyl group.

The alkyl moiety of a phenyl (C_{1-4}) alkyl group may be for example a methyl or ethyl moiety.

In one class of compounds of formula (I), the group R_1 may be a C_{1-6} alkyl, phenyl or phenyl(C_{1-4})alkyl group.

In general, the group R_1 is preferably a methyl or phenyl group.

n in the compounds of formula (I) may be an integer 3,4 or 5, but is preferably an integer 2.

A preferred class of compounds represented by the general formula (I) is that wherein R_2 represents a hydrogen atom. A further preferred class of compounds is that in which R_3 represents a hydrogen atom.

A still further preferred class of compounds is that in which R_4 and R_5 which may be the same or different each represents a hydrogen atom or a methyl or ethyl group. It is preferred that the total number of carbon atoms in R_4 and R_5 does not exceed two.

A particularly important compound according to the invention is: N-[2-[3-[2-(methylamino)ethyl]-1*H*-indol-5-yl]ethyl]methanesulphonamide and its physiologically acceptable salts and solvates (e.g. hydrates).

Suitable physiologically acceptable salts of the indoles of general formula (I) include acid addition salts formed with inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, oxalates, tartrates, citrates, fumarates, maleates, succinates, and sulphonates e.g. mesylates. Other salts may be useful in the preparation of compounds of formula (I) e.g. creatinine sulphate adducts.

It will be appreciated that the invention extends to other physiologically acceptable equivalents

of the compounds according to the invention, i.e. physiologically acceptable compounds which are converted *in vivo* into the parent compound. Examples of such equivalents include physiologically acceptable, metabolically labile N-acyl derivatives.

Compounds of the invention selectively constrict the carotid arterial bed of the anaesthetised dog, whilst having a negligible effect on blood pressure. Their selective vasoconstrictor action has been demonstrated *in vitro*.

Compounds of the invention are useful in treating pain resulting from dilatation of the carotid vascular bed, in particular migraine and cluster headache.

Accordingly, the invention also provides a pharmaceutical composition adapted for use in human medicine which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof and formulated for administration by any convenient route. Such compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily ester or ethyl alcohol); and preservatives (e.g. methyl or propyl-*p*-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative.

The compositions make take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for oral, parenteral, buccal or rectal administration to man (of average bodyweight e.g. about 70kg) for the treatment of migraine is 0.1 to 100mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

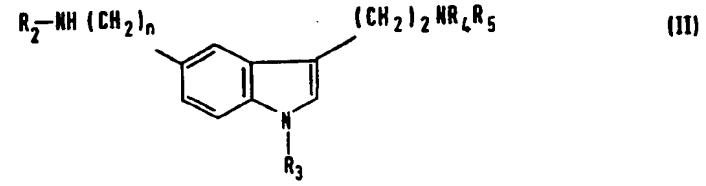
For oral administration a unit dose will preferably contain from 2 to 50mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.2 to 5mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 to 2 mg of a compound of the invention and each dose administered via capsules or cartridges in an inhaler or insufflator contains 0.2 to 20mg. The overall daily dose by inhalation will be within the range 1mg to 100mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and anti-nauseants.

According to another aspect of the invention, compounds of formula (I), and physiologically acceptable salts or solvates (e.g. hydrates) thereof, may be prepared by the general methods outlined below. In the following processes, R_1, R_2, R_3, R_4, R_5, A and n are as defined for the general formula (I) unless otherwise specified.

According to one general process (A), a compound of general formula (I) may be prepared by reacting a compound of general formula (II):



(II)

or a salt thereof (for example, an organic or inorganic acid addition salt such as the hydrochloride, hydrobromide, maleate, sulphate or creatinine sulphate adduct) or an N-silyl derivative thereof or a protected derivatives thereof with a reagent serving to introduce the group R_1A.

Suitable reagents which serve to introduce to group R_1A include acids of the general formula R_1AOH or acylating agents corresponding thereto.

Acylating agents which may conveniently be used in the above process include acid halides (for example carboxylic acid chlorides and sulphonyl chlorides), alkyl esters, (for example the methyl or ethyl ester), activated esters (for example the 2-(1-methylpyridinyl)ester), symmetrical anhydrides, mixed anhydrides or other activated carboxylic acid derivatives such as those conveniently used in peptide synthesis.

The process may be effected in a suitable aqueous or non-aqueous reaction medium, conveniently at a temperature of from −70 to +150°C. Thus the process using an acid halide, an activated ester or an anhydride may be effected in a suitable reaction medium such as an amide (e.g. N,N-dimethylformamide) or hexamethylphosphoramide, an ether (e.g. tetrahydrofuran), an ester (e.g. ethyl acetate) a nitrile (e.g. acetonitrile), a haloalkane (e.g. dichloromethane) or mixtures thereof, optionally in the presence of an organic base, for example a tertiary amine such as triethylamine or pyridine, or an inorganic base such as potassium carbonate or sodium bicarbonate. The organic base may also serve as a reaction solvent. The reaction is preferably effected at a temperature of from −5 to +25°C.

The reaction using an alkyl ester may be effected in a suitable reaction medium such as an alcohol (e.g. methanol), an amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or mixtures thereof and conveniently at a temperature of from 0 to 100°C.

When A represents –CO– carboxylic acids of formula R_1COOH may also be used in the preparation of compounds of formula (I). The reaction is desirably conducted in the presence of a coupling agent for example N,N'-carbonyldiimidazole or a carbodiimide such as N,N'-dicyclohexylcarbodiimide. The reaction may be carried out in a suitable reaction medium such as a haloalkane (e.g. dichloromethane), a nitrile (e.g. acetonitrile), and amide (e.g. dimethylformamide) or an ether (e.g. tetrahydrofuran) conveniently at a temperature of from −50 to +50°C, preferably −5 to +30°C. The reaction may also be carried out in the absence of a coupling agent in a suitable reaction medium such as a hydrocarbon (e.g. toluene or xylene) conveniently at a temperature of from 50 to 120°C.

A compound of general formula (I) wherein R_1A represents –CHO may be prepared by heating a compound of general formula (II) with ethyl formate optionally in the presence of a solvent e.g. ethanol preferably under reflux.

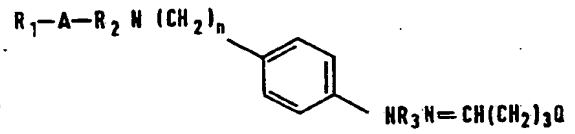
Compounds of general formula (II) are novel and comprise a further feature of the invention.

Compounds of general formula (II) wherein R_2 is a hydrogen atom may be prepared for example by reduction of a corresponding compound having an appropriate reducible group as the 5-position substituent, such as $-(CH_2)_{n-1}CN$ or a corresponding cyano-substituted alkenyl group. The reduction may be effected by catalytic hydrogenation, or with a reducing agent such as lithium aluminium hydride.

Such nitrile compounds are novel and constitute a further feature of the invention. These compounds may be prepared for example by cyclisation of an appropriate hydrazone, in an analogous manner to general process (B) described hereinafter. Alternatively, intermediates with a 5-(cyanoalkenyl) substituent may be prepared by reacting an appropriate indole-5-carboxaldehyde with a cyanoalkyl phosphonate.

Compounds of general formula (II) wherein R_2 is an alkyl group may be prepared for example by reduction of a corresponding nitrile in the presence of an amine R_2NH_2, or by reacting a compound of formula (II) wherein R_2 is a hydrogen atom with a suitable alkylating agent.

According to another general process (B), compounds of formula (I) may be prepared by the cyclisation of a compound of general formula (III):



(III)

wherein Q is the group NR_4R_5 (or a protected derivative thereof) or a leaving atom or group such as a halogen atom (e.g. chlorine or bromine) or an acyloxy group (e.g. a carboxylic or sulphonic acyloxy group such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, *p*-nitrobenzoyloxy, *p*-toluenesulphonyloxy or methanesulphonyloxy group).

The reaction may conveniently be effected in aqueous or non-aqueous reaction media, and at temperatures of from 20 to 200°C, preferably 50 to 125°C.

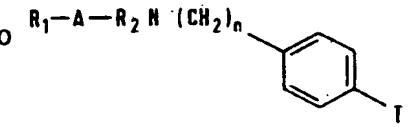
Particularly convenient embodiments of the process are described below.

When Q is the group NR_4R_5 (or a protected derivative thereof) the process is desirably carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethylether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons 1967).

Alternatively the cyclisation may be carried out in an aqueous or non-aqueous reaction medium, in the presence of an acid catalyst. When an aqueous medium is employed this may be an aqueous organic solvent such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) as well as mixtures of such solvents. The acid catalyst may be for example an inorganic acid such as concentrated hydrochloric or sulphuric acid or an organic acid such as acetic acid. (In some cases the acid catalyst may also act as the reaction solvent). In an anhydrous reaction medium, which may comprise for example one or more ethers (e.g. as previously described) or esters (e.g. ethyl acetate), the acid catalyst will generally be a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride.

When Q is a leaving atom or group such as a chlorine or bromine atom the reaction may be effected in an aqueous organic solvent, such as an aqueous alcohol (e.g. methanol; ethanol or isopropanol) in the absence of an acid catalyst, conveniently at a temperature of from 20 to 200°C, preferably 50 to 125°C. This process results in the formation of a compound of formula (I) wherein R_4 and R_5 are both hydrogen atoms.

According to a particular embodiment of this process compounds of formula (I) may be prepared directly by the reaction of a compound of general formula (IV):



(IV)

(where T is a group $-NR_3NH_2$)
or a salt thereof,
with a compound of formula (V):

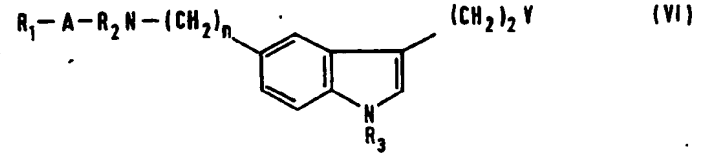
$OHC(CH_2)_3Q$ (V)

(wherein Q is as defined above) or a salt or protected derivative thereof (such as an acetal or ketal e.g. formed with an appropriate alkyl orthoformate or diol, or protected as a bisulphite addition complex) using the appropriate conditions as described above for the cyclisation of compounds of general formula (III). It will be appreciated that in this embodiment of the cyclisation process (B) a compound of general formula (III) is formed as an intermediate, and may be reacted *in situ* to form the desired compound of general formula (I).

Compounds of general formula (III) may, if desired, be isolated as intermediates during the process for the preparation of compounds of formula (I) wherein a compound of formula (IV), or a salt or protected derivative thereof, is reacted with a compound of formula (V), or a salt or protected derivative thereof, in water or in a suitable solvent, such as an aqueous alcohol (e.g. methanol) at a temperature of, for example, 20 to 30°C. If an acetal or ketal of a compound of formula (V) is used, it may be necessary to carry out the reaction in the presence of an acid (for example, acetic or hydrochloric acid).

Compounds of general formula (IV) may be prepared for example from the corresponding nitro (i.e. where T is NO_2) compounds, using conventional procedures.

A further general process (C) for preparing compounds of general formula (I) involves reacting a compound of general formula (VI):



(VI)

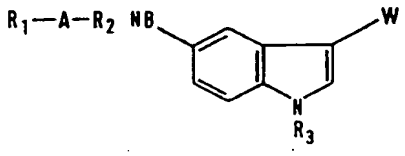
(wherein Y is a readily displaceable atom or group) or a protected derivative thereof, with an amine of formula R_4R_5NH.

The displacement reaction may conveniently be carried out on those compounds of formula (VI) wherein Y is a halogen atom (e.g. chlorine, bromine or iodine) or a group OR_6 where OR_6 is, for example, an acyloxy group which may be derived from a carboxylic or sulphonic acid; such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, *p*-nitrobenzoyloxy, *p*-toluenesulphonyloxy or methanesulphonyloxy group.

The displacement reaction may be conveniently effected in an inert organic solvent (optionally in the presence of water), examples of which include alcohols, e.g. ethanol; cyclic ethers, e.g. dioxan or tetrahydrofuran; acylic ethers e.g. diethylether, esters, e.g. ethyl acetate; amides, e.g. N,N-dimethylformamide; and ketones e.g. acetone or methylethyl ketone, at a temperature of from −10 to +150°C, preferably 20 to 50°C.

The compounds of general formula (VI) wherein Y is a halogen atom may be prepared by reacting a hydrazine of general formula (IV) with an aldehyde or ketone (or a protected derivative thereof) of formula (V) in which Q is a halogen atom, in an aqueous alcohol (e.g. methanol) containing an acid (e.g. acetic or hydrochloric acid). Compounds of formula (VI) wherein Y is the group OR_6 may be prepared from the corresponding compound where Y is a hydroxyl group by acylation with the appropriate activated species (e.g. anhydride or sulphonyl chloride) using conventional techniques. The intermediate alcohol may be prepared by cyclisation of a compound of formula (III) wherein Q is a hydroxyl group (or a protected derivative thereof) under standard conditions.

Compounds of formula (I) may also be prepared by another general process (D) involving reduction of a compound of general formula (VII):



(VII)

(wherein W is a group capable of being reduced to give the required $-(CH_2)_2NR_4R_5$ group or to give a protected derivative of $-(CH_2)_2NR_4R_5$; and B represents the group $-(CH_2)_n-$ as herein defined or a group capable of being reduced to $-(CH_2)_n-$) or a salt or protected derivative thereof.

The required $-(CH_2)_2-$ and $-NR_4R_5$ groups at the 3- position may be formed by reduction steps which take place separately or together in any appropriate manner.

Groups B which may be reduced to give the required group $-(CH_2)_n-$ include corresponding unsaturated groups, such as C_{2-5} alkenyl or alkynyl groups.

Examples of groups represented by the substituent W include $-(CH_2)_2NO_2$; $-CH=CHNO_2$; $-(CH_2)_2N_3$; $-CH_2CN$; $-CH_2CHO$; $-COCH_2Z$; $-CH_2CH=NOH$; $-CH(OH)CH_2NR_4R_5$; $-(CH_2)_2NR_4COR'_5$; $-COCONR_4R_5$ and $-CH_2COZ$ (wherein Z is an azido group or the group $-NR_4R_5$ or a protected derivative thereof and R'_5 is a hydrogen atom or a methyl or ethyl group or R'_5 represents the group OR_7 where R_7 is an alkyl or aralkyl group).

Groups which may be reduced to the $-(CH_2)_2-$ moiety include the corresponding unsaturated group and corresponding groups containing one or more hydroxyl groups or carbonyl functions.

Groups which may be reduced to the group $-NR_4R_5$ where R_4 and R_5 are both hydrogen include nitro, azido, hydroxyimino and nitrile groups.

In the latter case, reduction yields the group $-CH_2NH_2$ and thus provides a methylene group of the $-(CH_2)_2-$ moiety.

A compound of general formula (I) where R_5 is a hydrogen atom may also be prepared by reduction of a corresponding compound wherein R_5 is a benzyl group, e.g. with hydrogen in the presence of a catalyst, e.g. 10% palladium on charcoal.

The required $-NR_4R_5$ group wherein R_4 and/or R_5 are other than hydrogen may be prepared by reduction of a nitrile $-CH_2CN$ or an aldehyde $-CH_2CHO$ in the presence of an amine, R_4R_5NH.

A particularly suitable method for preparing a compound of formula (I) wherein R_4 and/or R_5 is

other than hydrogen is reductive alkylation of the corresponding compound wherein R_4 and/or R_5 represent hydrogen with an appropriate aldehyde or ketone (e.g. acetaldehyde or acetone) in the presence of a suitable reducing agent. Suitable reducing agents for use in this process include hydrogen in the presence of a metal catalyst, or an alkali metal borohydride or cyanoborohydride (for example, sodium borohydride or cyanoborohydride) using the conditions described below for the reduction of compounds of formula (VII). In some instances (e.g. for the introduction of the group R_5 where R_5 is ethyl) the aldehyde (e.g. acetaldehyde) may be condensed with the amine and the intermediate thus formed may subsequently be reduced using a suitable reducing agent.

The required $-NR_4R_5$ group wherein R_4 and/or R_5 are other than hydrogen may also be prepared by reduction of a corresponding amide group, e.g. of the formula $-(CH_2)_2NR_4COR'_5$ where R'_5 is as previously defined).

It will be appreciated that the choice of reducing agent and reaction conditions will be dependent on the nature of the groups W, B and other groups already present on the molecule. It will also be appreciated that when A represents –CO– the group W will not contain an amide function.

Suitable reducing agents which may be used in the above process for the reduction of compounds of formula (VII) wherein W represents, for example, the groups $-(CH_2)_2NO_2$; $-CH=CHNO_2$, $-(CH_2)_2N_3$, $-CH_2CN$, $-CH_2CH=NOH$ and $-CH(OH)CH_2NR_4R_5$ include hydrogen in the presence of a metal catalyst, for example Raney Nickel or a noble metal catalyst such as platinum, platinum oxide, palladium, palladium oxide or rhodium, which may be supported, for example, on charcoal, kieselguhr or alumina. In the case of Raney Nickel hydrazine may also be used as the source of hydrogen. This process may conveniently be carried out in a solvent such as an alcohol e.g. ethanol, an ether, e.g. dioxan or tetrahydrofuran, an amide, e.g. dimethylformamide or an ester e.g. ethyl acetate, and at a temperature of from −10 to +50°C, preferably −5 to +30°C.

The reduction process may also be effected on compounds of formula (VII) wherein W represents, for example, the groups $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-(CH_2)_2N_3$, $-CH(OH)CH_2NR_4R_5$ or $-COCH_2Z$ (where Z is as previously defined), using an alkali metal or alkaline earth metal borohydride or cyanoborohydride e.g. sodium or calcium borohydride or cyanoborohydride which process may conveniently be carried out in an alcohol such as propanol or ethanol or a nitrile such as acetonitrile, and at a temperature of from 10 to 100°C, preferably 50 to 100°C. In some instances the reduction using a borohydride may be carried out in the presence of cobaltous chloride.

When A represents $-SO_2-$, reduction of compounds of formula (VII) wherein W represents, for example, $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-(CH_2)_2N_3$, $-(CH_2)_2NR_4COR'_5$; $-CH_2CH=NOH$, $-CH(OH)CH_2NR_4R_5$; $-COCONR_4R_5$, $-CH_2COZ$ and $-COCH_2Z$ (wherein R'_5 and Z are as previously defined) may also be carried out using a metal hydride such as lithium aluminium hydride. This process may be carried out in a solvent, for example, an ether such as tetrahydrofuran, and conveniently at a temperature of from −10 to +100°C, preferably 50 to 100°C.

A particular embodiment of general process (D) includes the reduction of a compound of formula (VII) wherein W is the group $-CH_2CN$ for example, by catalytic reduction with hydrogen in the presence of a catalyst such as palladium on charcoal or rhodium on alumina, optionally in the presence of an amine HNR_4R_5.

Suitable reducing agents which may be used in the reduction of the group B include hydrogen in the presence of a metal catalyst. Appropriate metal catalysts and conditions for the reduction process are as described for the reduction of the group W.

The starting materials or intermediate compounds of formula (VII) may be prepared by analogous methods to those described in UK Published Patent Application No. 2035310, and 'A Chemistry of Heterocyclic Compounds—Indoles Part II', Chapter VI, edited by W J Houlihan (1972) Wiley Interscience, New York.

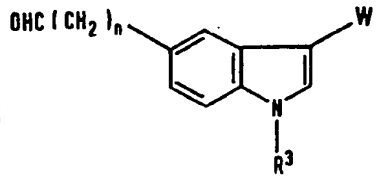
Compounds of formula (VII), wherein W is the group $-CH_2CHO$ may be prepared by oxidation (e.g. with Jones' reagent) of a compound of formula (VI) wherein Y is a hydroxyl group. A compound of formula (VII) wherein W is the group $-CH_2CH=NOH$ may be prepared by treatment of the corresponding aldehyde with hydroxylamine hydrochloride using standard conditions.

The intermediate compound of formula (VII) wherein W is the group $-(CH_2)_2N_3$ may be prepared from a compound of formula (VI) wherein Y is a halogen atom using standard procedures.

Standard reducing agents such as sodium borohydride may be used to prepare a compound of formula (VII) wherein W is the group $-CH(OH)CH_2NR_4R_5$ from the corresponding compound of formula (VII) wherein W is the group $-COCH_2NR_4R_5$.

A compound of formula (VII) wherein W is the group $-(CH_2)_2NR_4COR'_5$ may be prepared by acylation of the corresponding unsubstituted amine using conventional procedures.

The intermediate compounds of formula (VII) wherein B represents a C_{2-6} alkenyl group may be prepared by reacting a compound of general formula (VIII)



(VIII)

(wherein W is as defined for general formula (VII) and n is zero or an integer of from 1 to 3) with for example an appropriate phosphonium salt, using standard conditions.

According to a further general process (E) a compound of formula (I) according to the invention, or a salt or protected derivative thereof, may be converted into another compound of formula (I) using conventional procedures.

For example, a compound of general formula (I) wherein one or more of R_3, R_4 and/or R_5 are alkyl groups may be prepared from the corresponding compounds of formula (I) wherein one or more of R_3, R_4 and R_5 represent hydrogen atoms, by reaction with a suitable alkylating agent such as a compound of formula R_xL, (where R_x represents the desired R_3, R_4 or R_5 group and L represents a leaving atom or group such as a halogen atom or a tosylate group) or a sulphate $(R_x)_2SO_4$. Thus, the alkylating agent may be for example an alkyl halide (e.g. methyl or ethyl iodide), alkyl tosylate (e.g. methyl tosylate) or dialkylsulphate (e.g. dimethylsulphate).

The alkylation reaction may conveniently be carried out in an inert organic solvent such as an amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides such as sodium or potassium hydride, alkali metal amides such as sodium amide, alkali metal carbonates such as sodium carbonate or alkali metal alkoxide such as sodium or potassium methoxide, ethoxide or t-butoxide or tetrabutylammonium fluoride. When an alkyl halide is employed as the alkylating agent the reaction may also be carried out in the presence of an acid scavenging agent such as propylene or ethylene oxide. The reaction may be conveniently effected at a temperature of from −20° to 100°C.

Compounds of formula (I) wherein one or both of R_3 and R_4 represents propenyl may be prepared similarly, using an appropriate compound of formula R_xL or $(R_x)_2SO_4$.

According to another general process (F), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a rptoected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the reaction sequence for the preparation of a compound of general formula (I) or a salt thereof it may have been necessary or desirable to protect one or more sensitive groups in the molecule to avoid undesirable side reactions. For example, it may be necessary to protect the group NR_4R_5, wherein R_4 and/or R_5 represents hydrogen, by protonation or with a group easily removable at the end of the reaction sequence. Such groups may include, for example, aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl; or acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl or phthaloyl.

In some cases, it may also be desirable to protect the indole nitrogen with, for example, an aralkyl group such as benzyl.

Subsequent cleavage of the protecting group or groups may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal) or sodium and liquid ammonia; an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation. The phthaloyl group may be removed by hydrazinolysis (e.g. by treatment with hydrazine hydrate) or by treatment with a primary amine (e.g. methylamine).

As will be appreciated, in some of the general processes (A) to (E) described previously it may be necessary or desirable to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the previously described processes (A) to (E).

Thus, according to a further aspect of the invention, the following reactions in any appropriate sequence may if necessary and/or desired be carried out subsequent to any of the processes (A) to (E):

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate (e.g. hydrate) thereof.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I), with an appropriate acid, preferably with an equivalent amount or with creatinine sulphate in a suitable

solvent (e.g. aqueous ethanol).

The starting materials or intermediate compounds for the preparation of the compounds according to this invention may be prepared by analogous methods to those described in UK Published Patent Application No. 2035310.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. Thus, for example, the required group at the 5-position may be introduced before or after cyclisation to form the indole nucleus. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples. All temperatures are in °C.

Chromatography was carried out either in the conventional manner using silica gel (Merck, Kieselgel 60, Art. 7734) or by flash chromatography (W. C. Still, M. Kahn and A. Mitra, J. Org. Chem. 2933, *43*, 1978) on silica (Merck 9385) and thin layer chromatography (t.l.c.) on silica (Macherly-Nagel, Polygram) except where otherwise stated. The following abbreviations define the eluants used for chromatography and t.l.c: (A) Ethyl acetate-2-propanol-water-0.88 ammonia 25:15:8:2, (B) CH_2Cl_2-ethanol-0.88 ammonia 89:10:1, (C) Ethyl acetate, (D) CH_2Cl_2-ethanol-0.88 ammonia 83:5:15:1.5, (E) Ethyl acetate:cyclohexane 1:1, (F) Ether-methanol 9:1, (G) Ethyl acetate-methanol 9:1, (H) Ether, (I) Ethyl acetate-2-propanol-water-0.88 ammonia 200:15:8:2, (J) Ethyl acetate-2-propanol-water-0.88 ammonia 100:15:8:2, (K) Ethyl acetate-2-propanol-water-0.88 ammonia 50:15:8:2, (L) CH_2Cl_2-ethanol-0.88 ammonia 87:12:1.2, (M) CH_2Cl_2-ethanol-0.88 ammonia 95:5:0.5, (N) CH_2Cl_2-ethanol-0.88 ammonia 91:8:0.8.

Intermediates were routinely checked for purity by t.l.c. employing u.v. light for detection and spray reagents such as potassium permanganate ($KMnO_4$). In addition indolic intermediates were detected by spraying with aqueous ceric sulphate (CeIV) and tryptamines by spraying with a solution of iodoplatinic acid (IPA) or ceric sulphate.

Proton (^1H) nuclear magnetic resonance (n.m.r.) spectra were obtained either at 90MHz using a Varian EM 390 instrument or at 250MHz using a Bruker AM or WM 250 instrument. s=singlet, d=doublet, t=triplet, m=multiplet and q=quartet.

Intermediate 1

4-Hydrazinobenzeneacetonitrile hydrochloride

A solution of sodium nitrite (4.0g) in water (34ml) was added dropwise at −5° to −2° to a suspension of 4-aminobenzeneacetonitrile (7.6g) in concentrated hydrochloric acid (80ml), and stirring was continued at −2° for 20min. The mixture was filtered and the filtrate added dropwise at 0° to 5° to a solution of tin (II) chloride dihydrate (65g) in concentrated hydrochloric acid (130ml). The mixture was allowed to warm to room temperature overnight (17h), and the precipitate was filtered off, washed with concentrated hydrochloric acid, cold absolute ethanol, and dry ether, and dried to give the *title salt* as a powder (6.05g), m.p. 207–210° (foams).

Intermediate 2

3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-acetonitrile

A mixture of Intermediate 1 (3.15g) and 4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl) butanal diethyl acetal (4.95g) in aqueous acetic acid (25%, 150ml) was heated at reflux for 2h, cooled, and the precipitate filtered off, washed with water (2×20ml), then ether (100ml). The crude product was triturated with ethyl acetate to give the *title compound* as a solid (3.2g) m.p. 185–186°.

Intermediate 3

2-[2-[5-(2-Aminoethyl)-1H-indol-3-yl]ethyl]-1H-isoindole-1,3-(2H)-dione sulphate

A suspension of Intermediate 2 (0.96g) in methanol (100ml) containing concentrated sulphuric acid (0.58g) was hydrogenated over PdO on charcoal (50% aqueous paste, 0.96g) at room temperature and 70 p.s.i. for 24h. The catalyst was filtered off, washed with methanol and the filtrate evaporated to dryness to give the *title compound* as an oil (1.4g).

Intermediate 4

2-[2-[5-(2-Aminoethyl)-1H-indol-3-yl]ethyl]-1H-isoindole-1,3-(2H)-dione hydrochloride

A solution of Intermediate 2 (1.5g) in methanol (400ml) containing concentrated hydrochloric acid (0.6ml) was hydrogenated over PdO on charcoal (50% aqueous paste, 3.0g) at room temperature and pressure for 24h. The catalyst was filtered off, washed with methanol and the filtrate evaporated to dryness to give the *title compound* as a foam (1.2g). T.l.c. (A) Rf 0.6.

Intermediate 5

3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-carboxaldehyde quarter hydrate

Raney nickel (about 2g) was added to a stirred solution of 3-[2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl]-1*H*-indole-5-carbonitrile (4.98g) and sodium hypophosphite (10.06g) in pyridine (100ml), water (50ml) and acetic acid (50ml). The mixture was heated at about 50° for 6h, periodically adding further Raney nickel (5×about 2g). After cooling, the mixture was filtered, and the filtrate was diluted with water (1250ml) and extracted with ethyl acetate (3×500ml). The combined organic extract was washed with hydrochloric acid (2N; 2×500ml), dried ($MgSO_4$), evaporated *in vacuo*, and azeotroped with toluene (2×100ml), affording the *title aldehyde* as a solid (4.6g). A sample (0.53g) was purified by chromatography (C) affording the pure *title aldehyde* as a solid (0.49g), m.p. 202–203°.

Intermediate 6

(E)-3-[3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indol-5-yl]-2-propenenitrile

A solution of diethyl cyanomethylphosphonate (1.6ml) in dry tetrahydrofuran (THF; 40ml) was added slowly to a stirred suspension of NaH (80%; 0.3 g) in THF (40ml) under nitrogen. After 10 min a solution of Intermediate 5 (1.70g) in THF (40ml) was added to the resulting clear solution and the mixture was stirred at room temperature for 19h. The solution was then partitioned between hydrochloric acid (1N; 200ml) containing NaCl (50g) and ethyl acetate (3×150ml). The combined organic extract was dried ($MgSO_4$), and evaporated to dryness to give a solid (1.53g) which was purified by chromatography (E) affording the *title compound* as a crystalline solid (1.13g) m.p. 232–234°.

Intermediate 7

4-[2-[4-(Dimethylamino)butylidene]hydrazino]benzeneacetonitrile

4,4-Diethoxy-N,N-dimethylbutanamine (9.45g) was added to a stirred suspension of Intermediate 1 (9.2g) in deionized water (200ml) at room temperature under nitrogen, 2N hydrochloric acid (22ml) was added (pH 2), and stirring was continued at room temperature for 5h. The clear solution was basified with 8% aqueous $NaHCO_3$ (200ml) and extracted with $CHCl_3$ (3×200ml). The organic layers were dried ($MgSO_4$) and evaporated to give the *title compound* as an oil (15.6g). T.l.c. (Silica, B) Rf 0.35.

Intermediate 8

3-[2-(Dimethylamine)ethyl]-1H-indole-5-acetonitrile oxalate

Intermediate 7 (15.4g) was heated under reflux with polyphosphate ester (108g) in $CHCl_3$ (200ml) with stirring under nitrogen for 8 min. The mixture was poured onto ice, 8% aqueous $NaHCO_3$ (500ml) was added, and after 20 min stirring the layers were separated and the aqueous layer extracted with $CHCl_3$ (3×400ml). The aqueous layer was further basified to pH 9 with 2N Na_2CO_3 (200ml), solid NaCl was added, and the mixture was extracted with $CHCl_3$ (3×400ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give an oil (40.2g). The oil was partitioned between ethyl acetate (200ml) and 2N hydrochloric acid (4×40ml); the aqueous layers were basified (200ml 2N and 20ml 5N NaOH) and extracted with ethyl acetate (4×100 ml). The latter organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give an oil (9.3g). Purification by flash chromatography (B and D) gave a first crop (1.91g) as an oil and a second crop (4.0g) also as an oil. The second crop oil was dissolved in hot methanol (10ml), and oxalic acid (1.59g) in hot methanol was added. On cooling, crystals were deposited and after cooling in ice the crystals were filtered off, washed with methanol and dried to give the *title compound* (4.0g) m.p. 183.5–187°.

Intermediate 9

N^3,N^3-Dimethyl-1H-indole-3,5-diethanamine dioxalate

Intermediate 8 (3.17g) was partitioned between 8% aqueous $NaHCO_3$ (100ml) and CH_2Cl_2 (3×80ml) and the organic layers were dried ($MgSO_4$) and evaporated to give the free base as an oil (2.41g). The oil was hydrogenated at 45° and 70psi over 5% rhodium on alumina (1.0g) in 7% w/w ethanolic ammonia (200ml) for 15.5h. The catalyst was filtered off and the solvent evaporated to give an oil (2.58g). A portion (1.37g) of the soil was dissolved in methanol (6ml), and oxalic acid (1.12g) was added in methanol (2ml). Addition of dry ether (80ml) gave a gum, which was triturated with dry ether to afford the *title compound* as a solid (1.79g) m.p. 160–170° (foams).

Intermediate 10

N^3,N^3-Dimethyl-1H-indole-3,5-diethanamine dihydrochloride

Intermediate 8 (2.40g) was hydrogenated at 55psi over 10% palladium on charcoal (50% paste with water; 1.2g initially; a further 2.4g added after 25h and 1.2g after 70h) in ethanol (240ml) containing concentrated hydrochloric acid (2.4ml) for 138h. The catalyst was filtered off and the solvent evaporated to give a foam (2.81g), a sample (about 0.7g) of which was

partitioned between saturated aqueous Na_2CO_3 (100ml) and butanone (3×70ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give an oil (0.57g). A sample (169ml) of the oil was purified by flash chromatography to give an oil (46mg). T.l.c. (A) Rf 0.35.

Example 1

N-[2-[3-(2-Aminoethyl)-1H-indol-5-yl]ethyl]methanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1).

(i) *N-[2-[3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indol-5-yl]ethyl]methanesulphonamide*

A solution of Intermediate 3 (1.4g) in pyridine (10ml) at 5° was treated with methanesulphonyl chloride (0.46ml). After 24h at room temperature the mixture was poured onto concentrated hydrochloric acid (20ml) and ice (100g). The resulting solid was collected and purified by chromatography (F) to give the *title compound* as a foam (0.45g). T.l.c. (C) Rf 0.2

(ii) *N-[2-[3-(2-Aminoethyl)-1H-indol-5-yl]ethyl]methanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1)*

A solution of the product of stage (i) (0.29g) in ethanol (5ml) and tetrahydrofuran (2ml) was treated with hydrazine hydrate (0.2ml) and heated at reflux for 3h. After cooling the solution was evaporated to dryness, and the resulting solid was partitioned between ethyl acetate (50ml) and a saturated solution of K_2CO_3 (10ml). The aqueous layer was extracted with ethyl acetate (3×50ml), and the organic layer was dried ($MgSO_4$) and evaporated, giving an oil. This was dissolved in a hot mixture of ethanol/water (9:1, 20ml) and treated with an aqueous solution of creatinine and sulphuric acid (1:1, 2M, 0.3ml). On cooling the *title compound* crystallised (0.16g) m.p. 209–210°.

N.m.r. δ (D_2O) includes 2.8–3.5 (14H,m,–$CH_2CH_2NHSO_2Me$ and $CH_2CH_2NH_2$ and creatinine N-*Me*); 7.2 (1H,dd, indole -6) and 7.5–7.7 (2H,m, indole -4 and indole -7).

Example 2

N-[2-[3-[2-(Methylamino)ethyl]-1H-indol-5-yl]ethyl]methane sulphonamide, compound with creatinine, sulphuric acid and water (2:2:2:1)

(i) *N-[2-[3-[2-[Methylsulphonyl)amino]ethyl]-1H-indol-5-yl]ethyl]-formamide quarter hydrate*

A solution of the product of Example 1 as the free base (0.98g) in ethyl formate (50ml) and ethanol (50ml) was heated at reflux for 48h. The solvent was evaporated *in vacuo* and the residue partitioned between sulphuric acid (1N, 25ml) and ethyl acetate (50ml). The aqueous layer was extracted with ethyl acetate (25ml) and the combined organic extracts washed with brine (25ml), dried (Na_2SO_4) and evaporated *in vacuo* to give an oil. Purification by column chromatography (C and F) gave a foam. Trituration with ethyl acetate gave the *title compound* as a solid (0.15g) m.p. 89–91°.

(ii) *N-[2-[3-[2-(Methylamino)ethyl]-1H-indol-5-yl]ethyl]methane-sulphonamide, compound with creatinine, sulphuric acid, and water (2:2:2:1)*

A solution of the product of Stage (i) (0.6g) in dry tetrahydrofuran (THF) (20ml) was added dropwise under nitrogen, to a stirred suspension of $LiAlH_4$(0.7g) in dry THF (15ml). The mixture was heated at refulx for 5h, cooled in ice, and excess reagent decomposed by cautious addition of 10% water in THF. Brine (50ml) and ethyl acetate (100ml) were added, insoluble material filtered off, and the aqueous layer extracted with ethyl acetate (100ml). The combined organic extracts were washed with brine (50ml), dried (Na_2SO_4) and evaporated *in vacuo* to give an oil. The oil was dissolved in a hot mixture of ethanol (24ml) and water (3ml) and an aqueous solution of creatinine and sulphuric acid (1:1, 2M, 0.5ml) added. Filtration of the cooled mixture gave the *title compound* as a solid (0.37g) m.p. 222–224°. N.m.r. δ (D_2O) includes 2.6–3.6 (17H, m,CH_2CH_2NHMe and $CH_2CH_2NHSO_2Me$ and creatinine N-*Me*).

Example 3

N-[3-[3-(2-Aminoethyl)-1H-indol-5-yl]propyl]methanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1)

(i) *2-[2-[5-(3-Aminopropyl)-1H-indol-3-yl]ethyl]-1H-isoindole-1,3-(2H)-dione hemisulphate*

A solution of Intermediate 6 (0.95g) in methanol (550ml) and sulphuric acid (1.0ml) was hydrogenated at room temperature and pressure over pre-reduced 10% palladium on charcoal (50% aqueous paste; 2.08g) for 0.5h until hydrogen uptake (201ml) had ceased. Catalyst was filtered off, and the filtrate evaporated *in vacuo* to give an oil (4.7g). T.l.c. (A) Rf 0.3.

(ii) *N-[3-[3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indol-5-yl]propyl]methanesulphonamide*

A mixture of the product of Stage (i) (4.7g), methanesulphonyl chloride (1.0ml), $NaHCO_3$ solution (8%; 300ml) and ethyl acetate (250ml) was stirred vigorously at room temperature for

24h, adding further methanesulphonyl chloride (1.0ml) after 17h. The mixture (which contained an insoluble solid) was separated, and the aqueous phase was further extracted with ethyl acetate (2×200ml). The combined organic extract was washed with hydrochloric acid (2N; 200ml), dried ($MgSO_4$), and evaporated, affording an oil (0.49g), which was purified by chromatography on a silica column (H). On allowing appropriate fractions to stand briefly, *title compound* crystallised as a solid (0.1g) m.p. 165–167°.

(iii) *N-[3-[3-(2-Aminoethyl)-1H-indol-5-yl]propyl]methanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1)*

A solution of the product of Stage (ii) (0.48g) in ethanol (100ml) was treated with hydrazine hydrate (1.0ml) and heated at reflux for 1h 20min. After cooling, the solution was evaporated *in vacuo* and azeotroped with ethanol (2×50ml) to give a solid, which was partitioned between Na_2CO_3 solution (2N; 100ml) and ethyl acetate (3×100ml). The combined organic extract was dried ($MgSO_4$) and evaporated to dryness, giving an oil which was dissolved in a hot mixture of ethanol (64ml) and water (8ml) and an aqueous solution of creatinine and sulphuric acid (1:1, 2M, 0.56ml) added. On cooling, the *title salt* crystallised (0.43g) m.p. 212–214°.
N.m.r. δ (DMSO-d_6) includes 2.6–3.2(14H,m,$CH_2CH_2CH_2$, $NHSO_2Me$, $CH_2CH_2NH_2$ and creatinine N-*Me*); 6.8–7.5 (4H,m,aromatics); and 10.9 (1H,d,indole-1).

Example 4

N-[2-[3-(2-Aminoethyl)-1H-indol-5-yl]ethyl]acetamide, compound with creatinine, sulphuric acid and water (10:12:11:20)

(i) *N-[2-[3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indol-5-yl]ethyl]acetamide quarter hydrate*

A solution of Intermediate 4 (0.3g) in pyridine (10ml) was cooled in an ice bath, and treated dropwise with stirring with acetic anhydride (0.3ml). The solution was stirred at room temperature for 1h, diluted with water (15ml) and stirred for 15 min. The resulting solution was poured into hydrochloric acid (2N, 50ml), and extracted with ethyl acetate (2×50 ml). The combined extracts were washed with 2N hydrochloric acid (50ml), 2N Na_2CO_3 (50ml), dried (Na_8SO_4) and evaporated *in vacuo* to give a foam which was purified by chromatography (C) to give the *title compound* as a solid (0.125g) m.p. 165–168°.

(ii) *N-[2-[3-(2-Aminoethyl)-1H-indol-5-yl]ethyl]acetamide, compound with creatinine, sulphuric acid and water (10:12:11:20)*

A solution of the product of Stage (i) (0.5g) in ethanol (100ml) containing hydrazine hydrate (1.0ml) was heated at reflux for 3h, cooled, evaporated *in vacuo*, and re-evaporated with ethanol (2×20ml). The resulting solid was partitioned between Na_2CO_3 solution (2N, 100ml) and ethyl acetate (2×100ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*, to give an oil which was dissolved in a hot mixture of ethanol (16ml) and water (2ml) and treated with an aqueous solution of creatinine and sulphuric acid (1:1, 2M, 0.5ml). On cooling, the *title salt* crystallised (0.3g) m.p. 211–214°.
N.m.r. $\delta(D_2O)$ includes 2.95 (3H,s,NHCO*Me*); and 2.7–3.6 (11H,m,CH_2CH_2NHCO, $CH_2CH_2NH_2$ and creatinine N-*Me*).

Example 5

N-[2-[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]ethyl]acetamide oxalate

Intermediate 10 (0.4g) was added at room temperature to a stirred solution of triethylamine (0.55ml) in dry tetrahydrofuran (15ml), under nitrogen, and stirring was continued at room temperature for 5 min. The mixture as cooled to 0°, acetic anhydride (0.15ml) was added, and stirring was continued for 4h between 0° and 10°. The mixture was partitioned between saturated Na_2CO_3 solution (65ml) and butanone (3×50ml); the organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give an oil (0.64g). Purification by flash chromatography (B and D) gave an oil (139mg) which was dissolved in methanol (2ml) and combined with a further sample (57mg) which had been similarly prepared. Oxalic acid (77mg) in methanol (0.5ml) was added. Addition of dry ether gave a precipitate which was filtered off, washed with dry ether and dried to give the *title compound* as a solid (205mg), m.p. 85–93° (foams).
N.m.r. δ(DMSO) includes 1.81 (3H,s,NHCO*Me*); 2.7–3.0 (8H,m,NMe_2 and CONHCH$_2$$CH_2$); 3.08 (2H,t,$CH_2CH_2NMe_2$); 7.98 (1H,t,CONH) and 10.9 (1H,d,indole-1).

Example 6

N-[2-[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]ethyl]methanesulphonamide oxalate

Intermediate 10 (0.905g) was added to a stirred solution of triethylamine (1.26ml) in dry CH_2Cl_2 (50ml) at room temperature under nitrogen, and stirring was continued at room temperature for 5 min. Methanesulphonyl chloride (0.282ml) was added with cooling to 0°, and the mixture was allowed to warm to room temperature with stirring for 5h. The mixture was poured

into 2N Na_2CO_3 solution (60ml) and extracted with CH_2Cl_2 (3×50ml); the organic layers were dried ($MgSO_4$) and evaporated to give a gum (0.85g). Purification by short path chromatography (B,D,I,J, and K) gave an oil (65mg), which was dissolved in methanol (1ml). Oxalic acid (25mg) in methanol (0.5ml) was added. Addition of dry ether gave a precipitate which was washed with dry ether and dried to give the *title salt* as a solid (38mg), m.p. 159–165° (foams).
N.m.r. δ(DMSO) includes 2.9–3.0 (11H,m,N*Me*$_2$ and *Me*$SO_2NHCH_2CH_2$); 3.0–3.4 (6H,m,$CH_2CH_2NMe_2$ and SO_2NHCH_2); 7.15 (1H,t,SO_2NH) and 10.93 (1H,d,indole-1).

Example 7

N-[2-[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]ethyl]benzamide oxalate

Benzoyl chloride (0.53ml) was added to a stirred solution of Intermediate 9 as the free base (0.95g) and triethylamine (0.7ml) in dry CH_2Cl_2 (40ml) at room temperature under nitrogen, and stirring was continued at room temperature for 1h 40 min. The mixture was washed with 8% aqueous $NaHCO_3$ (20ml) and water (2×20ml), dried ($MgSO_4$) and the solvent evaporated. The resulting oil (1.47g) was combined with another portion prepared similarly, and purified by flash chromatography (B and L) to give a foam whcih was dissolved in methanol (2ml) and a solution of oxalic acid (230mg) in methanol (1ml) was added. Addition of dry ether (80ml) gave a precipitate which was washed with dry ether and dried to give the *title salt* as a solid (0.873g) m.p. 158–160°.
N.m.r. δ (DMSO) includes 2.80 (6H,s,N*Me*$_2$); 2.95 (2H,t,$CONHCH_2CH_2$); 3.06 (2H,m,$CH_2CH_2NMe_2$); 3.55 (2H,q,$CONHCH_2CH_2$); 7.44–7.6 (4H,m,phenyl (*m* and *p*) and indole-4); 8.63 (1H,t,CO*NH*) and 10.95 (1H,d,indole-1).

Example 8

N-[2-[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]ethyl]benzenesulphonamide oxalate

Benzenesulphonyl chloride (0.61ml) was added to a stirred solution of Intermediate 9, as the free base (0.98g) and triethylamine (0.72ml) in dry CH_2Cl_2 (40ml) at room temperature under nitrogen, and stirring was continued at room temperature for 1h 40 min. The mixture was washed with 8% aqueous $NaHCO_3$ (20ml) and water (2×20ml), dried ($MgSO_4$) and evaporated to give a foam (0.90g). This was combined with similarly-prepared material and the combined samples purified by chromatography (M and N). The resulting foam (0.607g) was dissolved in methanol (2ml), and oxalic acid (154mg) in methanol (1ml) was added. Addition of dry ether (80ml) gave a precipitate which was washed by decantation with dry ether, filtered off, and dried to give the *title salt* as a solid (0.702g) m.p. about 80–90° (foams).
N.m.r. δ(DMSO) includes 2.7–2.85 (8H,m,N*Me*$_2$ and $SO_2NHCH_2CH_2$); 2.95–3.1 (6H,m,$SO_2NHCH_2CH_2$ and CH_2CH_2NMe); 7.37 (1H,brs,SO_2NH); 7.55–7.7 (4H,m,Ph (*m* and *p*) and indole-4); and 10.9 (1H,s,indole-1).

Example 9

(i) *N-[2-[3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indol-5-yl]ethyl]benzamide, compound with ethyl acetate (2:1)*

A solution of thionyl chloride (1.72ml) in dry tetrahydrofuran (20ml) was added dropwise under nitrogen to a stirred, ice-cooled solution of benzoic acid (1.41g) in a mixture of triethylamine (8.00ml) and dry tetrahydrofuran (80ml). The solution was stirred in ice for 1h, and Intermediate 4 (2.13g) was added and stirring continued for 0.75h. The resulting suspension was partitioned between 2N Na_2CO_3 (250ml) and ethyl acetate (2×250ml). The combined organic extracts were washed with water (2×250ml) and 2N Na_2CO_3 (250ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil (3.1g) was chromatographed (E). The required fractions were combined and concentrated *in vacuo* to give the *title compound* as a foam (0.92g) m.p. 75–82°.

(ii) *N-[2-[3-(2-Aminoethyl)-1H-indol-5-yl]ethyl]benzamide, compound with creatinine, sulphuric acid and water (1:1:1:1)*

A solution of hydrazine hydrate (0.90ml) and the product of stage (i) (0.67g) in ethanol (25 ml) was stirred at reflux for 3.5h and then left to cool. The resultant suspension was concentrated *in vacuo* and the residual solid was partitioned between 2N Na_2CO_3 (50ml) and ethyl acetate (3×50ml). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. The residual gum (0.47g) was dissolved in a hot mixture of ethanol (40ml) and water (5ml) and an aqueous solution of creatinine and sulphuric acid (1:1; 2M; 0.76ml) was added. The solid that crystallised on cooling was filtered off, washed successively with a mixture of ethanol and water (8:1; 27ml) and ethanol (10ml) and dried at 60° for 8h to give the *title compound* as a solid (0.60g) m.p. 228°–229.5°.
N.m.r. δ(D_2O) includes 3.0–3.25 (9H,m,$CONHCH_2CH_2$, $CH_2CH_2NH_2$ and creatinine N*Me*; 3.68 (2H,t,CH_2CH_2NHCO); and 7.4–7.64 (7H,m,phenyl, indole-4 and indole-7).

Example 10

(i) *N-[2-[3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indol-5-yl]ethyl]benzenesulphonamide*

A solution of benzenesulphonyl chloride (1.38ml) in dry dimethylformamide (25ml) was added dropwise under nitrogen to a stirred, ice-cooled suspension of Intermediate 4 (2.0g) in a mixture of triethylamine (3.0ml), dry tetrahydrofuran (50ml) and dry dimethylformamide (25ml) and stirring was continued for 2.75h. The suspension was then left at room temperature overnight, and partitioned between 2N Na_2CO_3 (500ml) and ethyl acetate (2×500ml). The combined organic extracts were washed with water (2×500ml) and 2N Na_2CO_3 (500ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residual foam (2.41g) was chromatographed (E). The required fractions were combined and concentrated *in vacuo* to give the *title compound* as a solid (0.73g) m.p. 183–184°.

(ii) *N-[2-[3-(2-Aminoethyl)-1H-indol-5-yl]ethyl]benzenesulphonamide, compound with creatinine, sulphuric acid, and water (1:1:1:1)*

A suspension of the product of Stage (i) (0.60g) and hydrazine hydrate (0.75ml) in ethanol (30ml) was stirred under reflux for 4.25h. The resultant suspension was evaporated *in vacuo* and the residual solid was partitioned between 2N Na_2CO_3 (25ml) and ethyl acetate (3×25ml). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. The residual gum (0.46 g) was dissolved in a hot mixture of ethanol (36ml) and water (4.5ml), and an aqueous solution of creatinine and sulphuric acid (1:1; 2M, 0.68ml) was added. The solid which crystallised on cooling was filtered off, washed with a mixture of ethanol and water (8:1, 2×5ml) and ethanol (2×5ml), and then dried *in vacuo* at 60° for 6h to give the *title compound* as a solid (0.48g) m.p. 216–217.5°.

N.m.r. δ(DMSO) includes 2.78 (2H,t,$SO_2NHCH_2CH_2$); 2.85–3.2 (9H,m,SO_2NHCH_2, $CH_2CH_2NH_2$ and creatinine N-*Me*); 7.2–7.4 (3H,m,indole-2, indole-7 and SO_2NH); 7.5–8.0 6H,m,phenyl and indole-4) and 10.9 (1H,s, indole-1).

The following examples illustrate pharmaceutical formulations according to the invention containing 4-(acetylamino)-N-[2-[3-[2-(dimethylamino)-ethyl]-1*H*-indol-5-yl]ethyl]benzeneacetamide oxalate as the active ingredient. Other compounds of the invention may be formulated in a very similar manner.

TABLETS FOR ORAL ADMINISTRATION
DIRECT COMPRESSION

	mg/tablet
Active ingredient	2.4
Calcium hydrogen phosphate B.P.*	95.10
Croscarmellose sodium USP	2.00
Magnesium stearate, B.P.	0.50
Compression weight	100mg

* of a grade suitable for direct compression

The active ingredient is sieved before use. The calcium hydrogen phosphate, croscarmellose sodium and active ingredient are weighed into a clean polythene bag. The powders are mixed by vigorous shaking then the magnesium stearate is weighed and added to the mix which is blended further. The mix is then compressed using a Manesty F3 tablet machine fitted with 5.5mm flat bevelled edge punches, into tablets with target compression weight of 100mg.

Tablets may also be prepared by other conventional methods such as wet granulation.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

INJECTION FOR INTRAVENOUS ADMINISTRATION

		mg/ml
Active ingredient		0.6mg
Sodium Chloride BP		as required
Water for Injection BP	to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or to facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

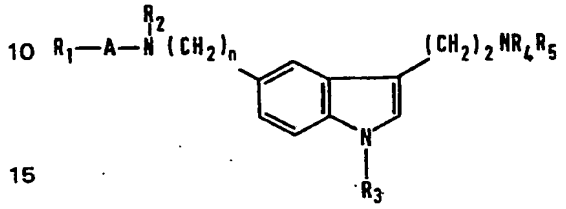
The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable

cycles.

Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

CLAIMS

1. Compounds of the general formula (I):



(I)

wherein

R_1 represents a hydrogen atom, a C_{1-6} alkyl or C_{3-7} cycloalkyl group; or a phenyl or phenyl (C_{1-4}) alkyl group;

R_2 represents a hydrogen atom or a C_{1-3} alkyl group;

R_3 represents a hydrogen atom or a C_{1-3} alkyl group;

R_4 and R_5 which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group or a 2-propenyl group;

A represents $-CO-$ or $-SO_2-$;

and n represents an integer from 2 to 5; (with the proviso that R_1 does not represent hydrogen when A represents $-SO_2-$) and physiologically acceptable salts and solvates thereof.

2. Compounds according to Claim 1, wherein, in the general formula (I), R_1 represents a C_{1-6} alkyl, phenyl or phenyl (C_{1-4}) alkyl group.

3. Compounds according to Claim 2, wherein, in the general formula (I), R_1 represents a methyl or phenyl group.

4. Compounds according to any of Claims 1 to 3, wherein, in the general formula (I), n represents the integer 2.

5. Compounds according to any of Claims 1 to 4, wherein, in the general formula (I), R_2 represents a hydrogen atom.

6. Compounds according to any of Claims 1 to 5, wherein, in the general formula (I), R_3 represents a hydrogen atom.

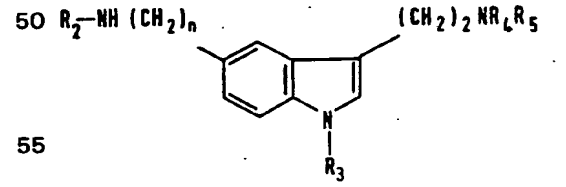
7. Compounds according to any of Claims 1 to 6, wherein, in the general formula (I), R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a methyl or ethyl group.

8. N-[2-[3-[2-(Methylamino)ethyl]-1*H*-indol-5-yl]methanesulphonamide and its physiologically acceptable salts and solvates.

9. A pharmaceutical composition comprising at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof together with one or more physiologically acceptable carriers or excipients.

10. A process for the preparation of a compound of general formula (I) as defined in Claim 1 or a physiologically acceptable salt or solvate thereof which comprises:

(A) reacting a compound of general formula (II):

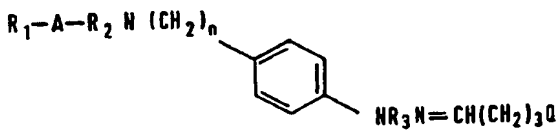


(II)

(wherein R_2, R_3, R_4, R_5 and n are as defined in Claim 1)

or a salt thereof, or an N-silyl derivative thereof or a protected derivative thereof, with a reagent serving to introduce the group R_1A (where R_1 and A are as defined in Claim 1); or

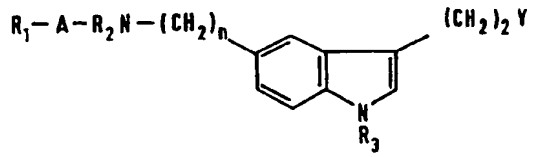
(B) cyclising a compound of general formula (III):



(III)

(wherein R_1, R_2, R_3, A and n are as defined in Claim 1 and Q is the group NR_4R_5 (where R_4 and R_5 are as defined in Claim 1) or a protected derivative thereof, or a leaving atom or group; or

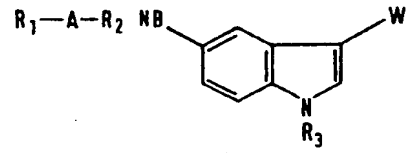
(C) reacting a compound or general formula (VI):



(VI)

(wherein R_1, R_2, R_3, A, Y and n are as defined in Claim 1 and Y is a readily displaceable atom or group) or a protected derivative thereof, with an amine of formula R_4R_5-NH (where R_4 and R_5 are as defined in Claim 1); or

(D) reducing a compound of general formula (VII):



(VII)

(wherein R_1, R_2, R_3 and A are as defined in Claim 1 and W is a group capable of being reduced to give the required $-(CH_2)_2NR_4R_5$ group, where R_4 and R_5 are as defined in Claim 1, or to give a protected derivative of $-(CH_2)_2NR_4R_5$ and B represents the group $-(CH_2)_n-$, where n is as defined in Claim 1, or a group capable of being reduced to $-(CH_2)_n-$) or a salt or protected derivative thereof; or

(E) in order to prepare one compound of general formula (I) as defined in Claim 1, or a physiologically acceptable salt or solvate thereof, subjecting another compound of general formula (I) or a salt or solvate thereof to an interconversion reaction; or

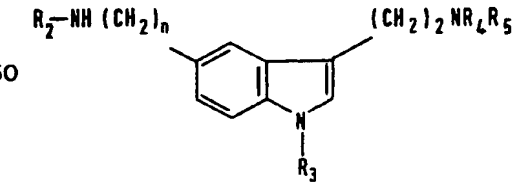
(F) subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups; and

if necessary and/or desired subjecting the compound resulting from any of processes (A) to (E) to one or two further reactions comprising;

(i) removing any protecting groups; and

(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

11. Compounds of general formula (II):



(II)

wherein

R_2 represents a hydrogen atom or a C_{1-3} alkyl group;

R_3 represents a hydrogen atom or a C_{1-3} alkyl group;

R_4 and R_5, which may be the same or different, each represents a hydrogen atom, a C_{1-3} alkyl group or a 2-propenyl group; and

n represents an integer from 2 to 5, and salts thereof.

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